Figure 1:

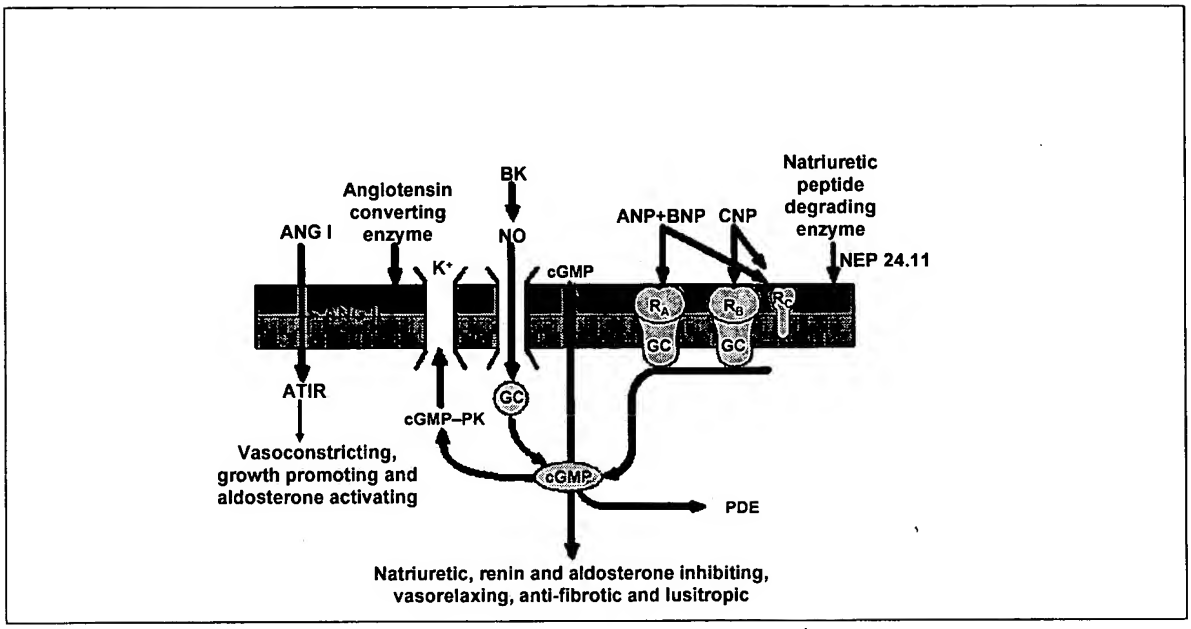
BK
Angiotensin converting enzyme
ANG I
NO
ANP+BNP
CNP
Natriuretic peptide degrading enzyme
NEP 24.11
K+
cGMP
R_A
R_B
R_C
GC
GC
ATIR
GC
cGMP–PK
Vasoconstricting, growth promoting and aldosterone activating
cGMP
PDE
Natriuretic, renin and aldosterone inhibiting, vasorelaxing, anti-fibrotic and lusitropic

Figure 2:

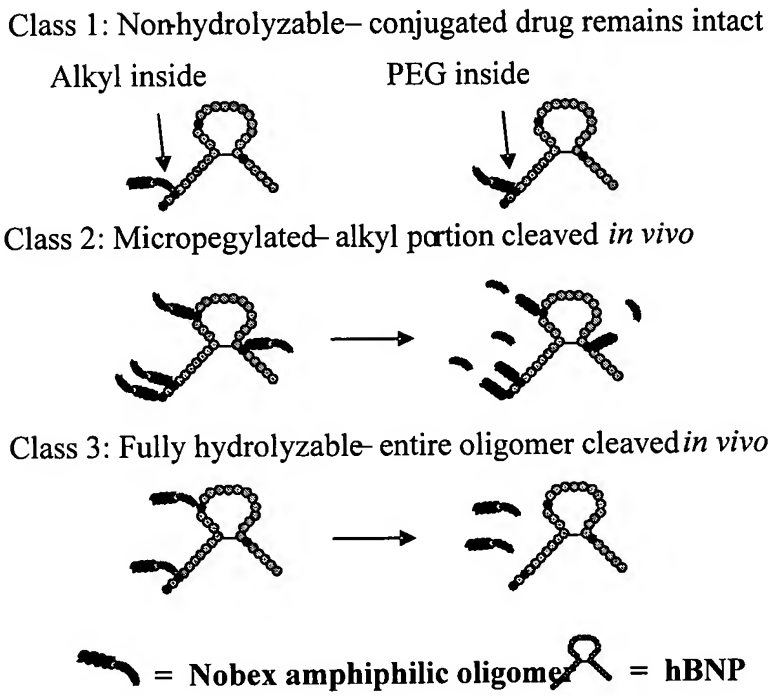
Class 1: Non-hydrolyzable– conjugated drug remains intact
Alkyl inside
PEG inside
Class 2: Micropegylated– alkyl portion cleaved *in vivo*
Class 3: Fully hydrolyzable– entire oligomer cleaved *in vivo*
= Nobex amphiphilic oligomer
= hBNP

Figure 3:

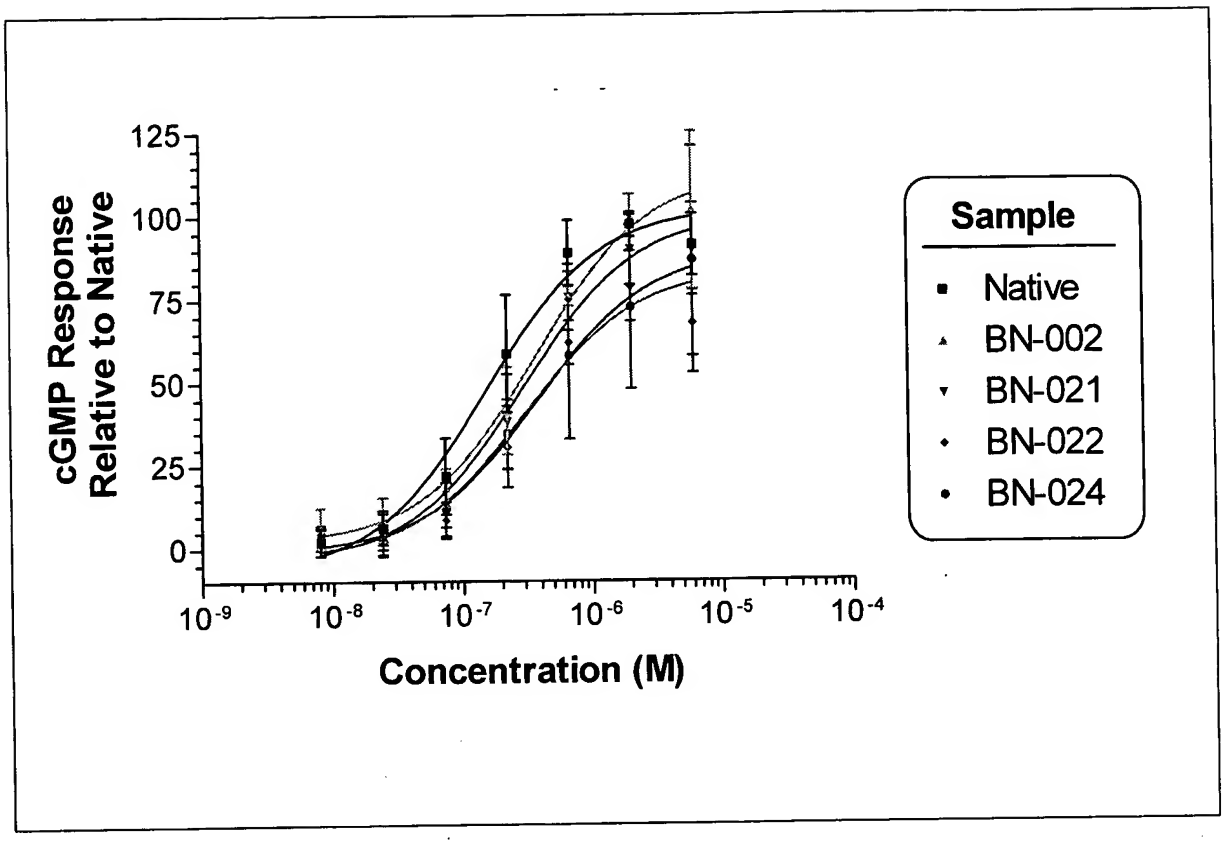
cGMP Response Relative to Native
125
100
75
50
25
0
10^{-9}
10^{-8}
10^{-7}
10^{-6}
10^{-5}
10^{-4}
Concentration (M)
Sample
Native
BN-002
BN-021
BN-022
BN-024

Figure 4:

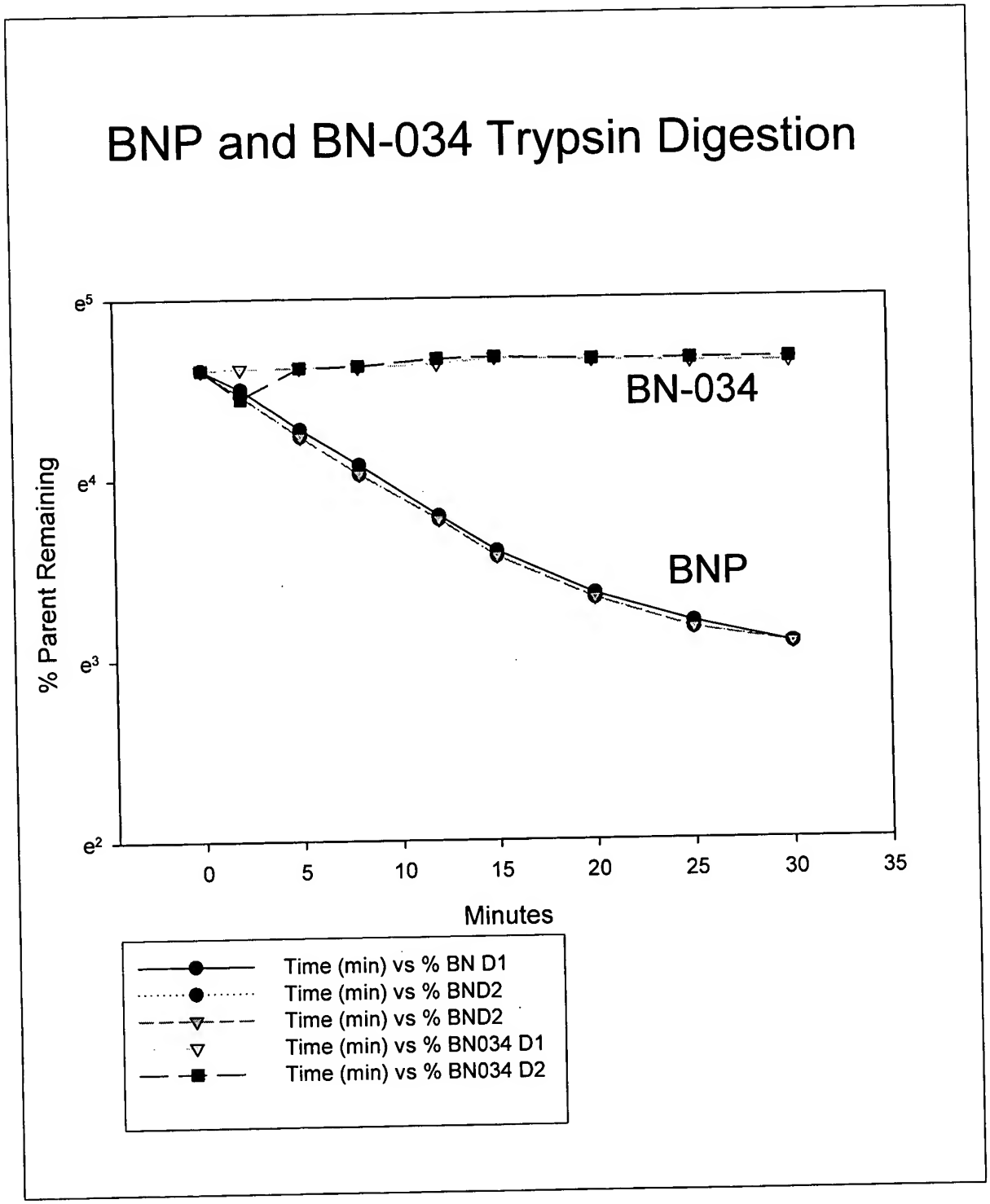
BNP and BN-034 Trypsin Digestion
% Parent Remaining
e5
e4
e3
e2
BN-034
BNP
0
5
10
15
20
25
30
35
Minutes
Time (min) vs % BN D1
Time (min) vs % BND2
Time (min) vs % BND2
Time (min) vs % BN034 D1
Time (min) vs % BN034 D2

Figure 5:

Figure 5: Plasma levels of hBNP conjugates at various times after oral dosing.